REMARKS

The Office Action dated March 21, 2005 has been carefully reviewed and the foregoing amendment and the following remarks are made in response thereto. In view of the amendment and the following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Applicants respectfully submit that no prohibited new matter has been introduced by the amendment. Support for the amendments to the claims can be found in the original claims, figures and throughout the specification as originally filed. Claim 21 has been amended to incorporate the term "whose expression levels are modulated under said disease conditions." Support for the amendment can be found at page 14, lines 4-7 of the specification. Claim 21 has also been amended to more particularly point out the steps of determining whether a subject has one of diseases described in the claim. Support for the amendment can be found at page 46, lines 14-17. As amended, claims 21, 34, 37-46 are current under consideration.

Summary of Final Office Action

1. Claims 21, 34 and 37-46 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

2. Claims 21 and 34-46 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner has maintained the rejections of claims 21, 34 and 37-46 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in a way to enable one skilled in the art to make or use the claimed invention.

The Examiner alleges that the specification has not provided sufficient guidance to enable the skilled artisan to diagnose a disorder by comparing the expression pattern of T lymphocytes from a subject to the expression profile of T lymphocytes from reference normal or inflammatory disease states or from other disease states (Office Action, page 4). More

specifically, the Examiner asserts that while Applicants teach more than 30 genes that can serve as markers of diseases, Applicants have not in fact taught any genes that are specifically associated with the occurrence of glomerulonopephritis or other sterile inflammatory diseases, immunodeficiency disorder, autoimmune disorder cancer or GVHD (Office Action, page 5).

Applicants respectfully disagree with the assertion of the Examiner with regard to the specific association of gene to the diseases. As explained in detail in the Applicant's previous communications, all those genes disclosed in the specification including the more than 30 gene represented in Figures 4 and 5 are pertinent to one or more diseases as claimed in the present invention. The specification teaches that the genes of interest in the expression profiles are genes whose expression levels are modulated under the relevant infection, disease, screening, treatment or other experimental conditions (see, for example, page 14, lines 4-7) or genes whose levels are modulated in a T lymphocyte population from a subject having a sterile inflammatory disease, autoimmune disorder, immunodeficiency disorder or T lymphocyte neoplasm (see, for example, page 45, Example 11). It is thus clear that the genes in a gene expression profile from T lymphocytes are specifically associated with the diseases to be diagnosed because the gene expression levels in the cells are modulated by the diseases.

Moreover, in an effort to advance prosecution of this application, Applicants have amended claim 21 to more particularly point out that the genes in the expression profiles are associated with the diseases. Thus, the present claims are directed to a method of diagnosing a sterile inflammatory disease, autoimmune disorder, immunodeficiency disease, cancer, or GVHD in a subject, comprising the steps of: preparing a first gene expression profile of at least five genes whose expression levels are modulated under said disease conditions of a T lymphocyte population from the subject; comparing the first gene expression profile to a second and third gene expression profiles to determine which expression profile most closely matches the expression profile prepared from the subject.

Applicants respectfully submit that in view of the foregoing arguments and the amendments, the claims fully comply with and satisfy all of the requirements of the first paragraphs of 35 U.S.C. § 112.

The Examiner further contends that the specification teaches genes that are up- or down-regulated only in activated or quiescent Jurkat cells, which is different from

establishing that these genes are up- or down-regulated in glomerulonopephritis or other specific disorders (Office Action, page 8). Applicants respectfully submit that the specification discloses more than genes up- or down-regulated in quiescent or activated Jurkat cells. The specification provides specific examples of diagnosing sterile inflammatory, autoimmune, or immunodeficiency disorders (see Example 13, page 46) and GVHD (see Example 14, page 47) by comparing the gene expression levels in T lymphocytes isolated from patients with various sterile inflammatory diseases. Therefore, contrary to the Examiner's assertion that the specification only teaches *in vitro* gene expression profile, the specification provides examples of comparing gene expression profiles of T lymphocytes obtained *in vivo* from patients.

The Examiner further contends that the specification has not taught one of skill in the art how to use the sequences set forth in Figures 4 and 5 to detect the expression of specific genes and that the sequences set forth in Figures 4 and 5 appear to be of unknown function and appear to represent small fragments of gene sequences. The Examiner alleges that undue experimentation would be required to use the disclosed sequences.

In response, Applicants respectfully submit that, as explained in detail in the Applicant's previous communications, the specification provides sufficient guidance for one of ordinary skill in the art to practice the invention using the gene sequences disclosed in Figures 4 and 5. The specification discloses that genes, such as those listed in Figures 4 and 5, can serve as markers for various T cells that have been activated by antigens, pathogens, or other inflammatory mediators. Similar gene expression profiles can be obtained from a subject to be diagnosed. The expression profile of the diagnosed subject can then be compared to the expression profile prepared from a patient having one of the diseases to determine if the expression profiles are similar as compared to a normal control, thereby diagnosing whether the subject has a sterile inflammatory disease, immunodeficiency disease, autoimmune disorder, *etc.* Applicants note that no claim recites the use of the sequences of Figures 4 and 5 and that the Examiner's focus on these sequences is misguided.

As for the Examiner's assertion that the sequences in Figures 4 and 5 appear to be of unknown function, Applicants respectfully assert that the identity or number of genes up- or down regulated in T cells in various disease states does not need to be disclosed to diagnose a sterile inflammatory disease, immunodeficiency disease, autoimmune disorder, *etc.* as

claimed. The instant claims merely involve diagnosing a disease by comparing the gene expression profiles. As claimed, the gene profiles may contain as few as five genes or as many as 1,000 or more genes. As long as the same genes are compared, one skilled in the art is able to determine whether the gene expression profile from a subject to be diagnosed closely matches that of a patient with the disease and subsequently make a correct diagnosis.

As for the Examiner's assertion that the sequences in Figures 4 and 5 represent small fragments of gene sequences, the Examiner's attention is directed to the instant claims that in no way recite the sequences of Figures 4 and 5.

For the purposes of argument, even if Figures 4 and 5 were to contain small fragments of gene sequences, the disclosure in the specification teaches that such gene sequence information may be utilized to diagnose various diseases as claimed. To doubt such disclosure in the specification, the Examiner has the initial burden to provide evidence to the contrary. It is well settled in the patent case law that a specification disclosure that contains a teaching of the manner and process of making and using the invention in terms that correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). Further, the burden is on the Examiner to come forth with evidence to establish a prima facie case of non-enablement. Ex parte Hitzeman, 9 U.S.P.Q. 2d 1801, 1822 (Pat. Off. Bd. App. 1988); In Re Armbruster, 185 U.S.P.Q. 152, 153 (C.C.P.A. 1975); In re Marzocchi, 169 U.S.P.Q. at 370. Applicants respectfully submit that the Examiner has not provided any scientific evidence whatsoever to show that one skilled in the art is not able to use small fragments of gene sequences to practice the present invention.

Finally, the Examiner contends that the specification does not provide sufficient guidance to enable the skilled artisan to diagnose a disease based on a finding of similar expression profiles. More specifically, the Examiner alleges that specification does not teach what would constitute a "similar" gene expression profile. The Examiner questions that, in a gene expression profile of 1000 genes, how many of these genes need to actually be informative in order to allow for the diagnosis of a disease (Office Action, page 11).

In response, Applicants respectfully traverse the rejection for the following reasons.

First, claim 21, as amended, recites the step of determining if the subject has one of the diseases by determining which expression profile most closely matches the expression profile prepared from the subject. It is thus clear that the gene expression profiles to be compared need only match closely to each other. Moreover, applicants respectfully submit that one of ordinary skill in the art at the time of the invention knows how to compare gene expression profiles to study diseases. Since preparation and comparison of gene expression profiles were well known and practiced in the art at the time of the invention, Applicants need not provide detailed description in the specification. It is a tenet of patent law that an applicant need not teach what the skilled artisan already knows. Instead, it is preferred that an applicant "omit what is known in the art." Hybritech Inc. v. Monoclonal Antibodies, 231 USPQ 81, 94 (Fed. Cir. 1986).

In support of the statement above, Applicants would like to direct the Examiner's attention to an article by Heller (Proc. Natl. Acad. Sci. USA, 94, 2150-2155 (1997), provided in Applicants' supplementary IDS filed March 14, 2005), published before the priority date of the subject application. For example, Heller states that it is feasible to simultaneously monitor differential expression of hundreds of genes with the cDNA microarray based system to analyze complex diseases such as rheumatoid arthritis (RA) (page 2154 first paragraph under DISCUSSION). By comparing the gene expression profiles of two disease states, Heller was able to determine that RA and inflammatory bowel disease (IBD) have distinct differences in gene expression patterns (page 2154, left column, second paragraph). Heller summarized that gene expression patterns obtained from cDNA microarray technology are well suited for profiling diseases (page 2155, last paragraph).

Applicants respectfully submit that one skilled in the art can prepare gene expression profiles of T lymphocytes from a control subject, a disease subject and a subject to be diagnosed, compare the expression levels of the genes in the profiles, and determine whether the subject to be diagnosed has the disease. Accordingly, it is urged that the Examiner's § 112 first paragraph rejection should be withdrawn and the claims allowed.

The Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 21, 34 and 37-46 remain rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention. More specifically, the Examiner asserts that the claims do not clearly set forth the relationship between the comparing and determining steps and do not clearly indicate how the comparison step results in the determination of the disease. Without conceding the correctness of the Examiner's rejection, claim 21 has been amended to recite that the diagnosis is made by determining which of the reference expression profiles most closely matches the expression profile prepared from the subject. As discussed above, one of skill in the art would be able to distinguish which expression profile closely matches and which gene expression profile has distinct differences in gene expression patterns from another expression profile. In light of the amendment, Applicants respectfully request reconsideration and withdrawal of the rejection.

Conclusion

Applicants respectfully request reconsideration of the subject application in view of the amendments to the claims and the above remarks. It is respectfully submitted that this application is now in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this amendment, the Examiner is requested to contact the Applicants' undersigned representative.

If there are any fees due in connection with the filing of this amendment, please charge the fees to our Deposit Account No. 50-310. If a fee is required for an extension of time under 37 C.F.R. 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

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